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EXAMINER

BERTOGLIO, VALARIE E

ART UNIT

PAPER NUMBER

1632

DATE MAILED: 05/31/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

10/799,372

Applicant(s)

MUMM ET AL.

Examiner

Valarie Bertoglio

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1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 01 May 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-18 is/are pending in the application.
- 4a) Of the above claim(s) 13-18 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-12 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 12 March 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_.
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_.

## **DETAILED ACTION**

### ***Election/Restrictions***

Applicant's election with traverse of Group I, claims 1-12 in the reply filed on 05/01/2006 is acknowledged. The traversal is on the ground(s) that no legal basis for restriction was presented. This is not found persuasive because Groups II-IV are drawn to distinct methods of using the product of Group I (see paragraph bridging pages 2-3 of the restriction requirement dated 03/31/2006; see MPEP 806.05(h)). Thus, the restriction requirement is maintained as the product can be used in materially different processes.

However, it is noted that the examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder

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in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.** Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Claims 13-18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 05/01/2006.

Claims 1-18 are pending and claims 1-12 are under consideration in the instant office action.

### ***Specification***

The disclosure is objected to because of the following informalities: The sentence at lines 7-9 of paragraph [000257] appears to be incomplete. It does not state what 14 repeats are fused to the carp  $\beta$ -actin promoter.

Appropriate correction is required.

### ***Claim Objections***

Claim 12 is objected to because of the following informalities: Claim 12 is grammatical incorrect in usage of the term “it’s” at line 6. The term should read “its”. Appropriate correction is required.

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Claims 2-11 are objected to because of the following informalities: Referring to “The” subject of a previous claim, rather than “A”, is proper format for a dependent claim. Accordingly, “A transgenic fish” in claims 2-11 should read “The transgenic fish”.

Appropriate correction is required.

***Claim Rejections - 35 USC § 112-1<sup>st</sup> paragraph***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9, 11 and 12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic fish selected from the group consisting of zebrafish and medaka whose genome comprises at least one transgene encoding an ablation-promoting moiety and/or a reporter moiety operably linked to a fish promoter or a coupled expression system encoding an ablation-promoting moiety and/or a reporter moiety wherein an expression driver is operably linked to a fish promoter, wherein the transgene is expressed in a reproducible spatial and temporal pattern and is inherited through the germline of the fish and for a method of making said fish using a transgene encoding an ablation-promoting moiety and/or a reporter moiety operably linked to a fish promoter, does not reasonably provide enablement for use of a non-fish promoter, use of a transgene that is not operably linked to a promoter or for skeletal, heart or cartilage-specific expression or a method of making the fish using any transgene. The specification does not enable any person skilled in the art to which it pertains, or

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with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The claims are drawn to a transgenic fish comprising a transgene encoding an ablation-promoting moiety. Claims 1-3 do not require the presence of an operably linked promoter. Claims 7-9 limit the type of promoter to be used to those specific for neural cell types (claim 7), skeletal and/or cartilage (claim 8) or heart (claim 9). Claim 11 requires that the regulatory sequence used be from a species (including non-fish species) other than that of the fish claimed. Claim 12 is drawn to a method of making the fish of claim 1 using any transgene.

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The specification teaches making transgenic zebrafish using a Gal4-UAS system comprising separate constructs comprising GAL4 operably linked to the goldfish  $\alpha$ -1-tubulin promoter, DsRed operably linked to a UAS and CFP-nitroreductase operably linked to a UAS. The resulting fish express DsRed and CFP-nitroreductase in neural cells (pages 67-68, paragraph [000243]). Upon exposure to metronidazole, nitroreductase expressing cells were eliminated. The specification also teaches making germline transgenic zebrafish using a gene encoding GFP-nitroreductase fused to a Fugu ChAT promoter (paragraph [000249] and [000262]). The specification also teaches a system comprising transgenic zebrafish transiently transfected with CFP-nitroreductase operably linked to a carp  $\beta$ -actin core promoter and 14 UAS repeats. A GAL4/VP16 driver (paragraphs [00257-000258]) can be introduced to direct gene expression wherein GAL4/VP16 is operably linked to a promoter. The specification specifically teaches an  $\alpha$ -1-tubulin-Gal4-VP16 driver. The specification does not teach any promoters specific to heart, skeletal or cartilage cells.

The art at the time of filing with respect to transgenic fish was that promoters of heterologous origin were not efficiently or effectively expressed (refer to Udvadia, 2003, **Dev. Biol.** 256, page 7, col.1, paragraph 4 ; Ju *et al.*, **Developmental Genetics**, 25 : 158-167, specifically page 159, col. 1, paragraph 1). In fact, it is thought that non-zebrafish promoters are often silenced when introduced into the genome of zebrafish (see Higashijima, 1997, **Dev. Biol.**, 192:289-299). Higashijima found that use of zebrafish derived promoters in zebrafish resulted in much more consistent expression with higher fidelity across a large number of independently derived lines (refer to paragraph bridging col. 1-2 of page 297). Therefore, it was recognized in the art that use of heterologous promoters in fish was highly unpredictable as to whether the

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transgene would be expressed, silenced, or expressed to a particular level and in a specific desired pattern.

Thus, the state of the art has established an unpredictability with respect to the activity of non-fish promoters in transgenic fish. Because the specification fails to provide guidance with respect to which non-fish promoters would be effective in carrying out the claimed invention, it would require undue experimentation to determine which promoters encompassed by the claims, other than fish promoters, could be effectively used in the claimed invention.

Claim 12 is not enabled for the full breadth because it is drawn to a method of making the fish of claim 1 wherein any transgene is used. Claim 1 requires a specific genus of transgenes and cannot be made using any transgene other than those encoding an ablation-promoting moiety and/or a reporter moiety operably linked to a fish promoter or a coupled expression system encoding an ablation-promoting moiety and/or a reporter moiety wherein an expression driver is operably linked to a fish promoter. Use of any transgene as claimed would not result in the claimed fish.

Claims 8 and 9 were not enabled at the time the invention was made because the specification and the art failed to teach any fish promoters that specifically express in the skeletal, cartilage or heart tissue. The zebrafish *cmlc2* promoter appears to have been the first heart specific promoter [Huang et al, **Dev Dynam**, 228:30-40, 2003] and was published after the filing of the instant application. No skeletal or cartilage-specific promoter cloned from fish has been made of record. The specification teaches fish neural-specific promoters, however, it does not provide the guidance necessary to carry out the claimed invention with skeletal, cartilage or heart-specific promoters. Therefore, it would require undue experimentation to determine what



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regulatory sequences to use to effectively drive heart, skeletal or muscle-specific expression in transgenic fish.

***Claim Rejections - 35 USC § 112-2<sup>nd</sup> paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 recites the limitation "the regulatory DNA sequence" in line 2. There is insufficient antecedent basis for this limitation in the claim. Claims 5-11 depend from claim 4.

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***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Valarie Bertoglio  
Examiner  
Art Unit 1632